



Ritvij Bowry and James C. Grotta

Contents

Introduction	368
Epidemiology	368
Etiology	368
Pathophysiology	368
Clinical Features	370
Diagnosis	370
Management	373
Pharmacologic	373
Non-pharmacologic	376
Prognosis	376
Conclusion	377
References	377

Abstract

Stroke and cancer have significant morbidity and mortality with heterogeneous risk factors. While conventional risk factors such as atherosclerosis and cardiac disease are important

mechanisms in the occurrence of stroke, cancer is an unconventional risk factor that leads to both ischemic and hemorrhagic stroke in a myriad of ways. Although cancer-associated strokes have unique underlying mechanisms, the clinical features, diagnosis, and management scheme are similar for non-cancer-associated strokes. Prognosis is complex and is dependent on the stage and type of cancer, expected treatment course, and stroke burden.

R. Bowry

Department of Neurosurgery, Division of Neurocritical care, McGovern Medical School, University of Texas Health Science Center, Houston, TX, USA
e-mail: Ritvij.Bowry@uth.tmc.edu

J. C. Grotta (✉)

Clinical Innovation and Research Institute, Memorial Hermann Hospital, Houston, TX, USA
e-mail: james.c.grotta@uth.tmc.edu

Keywords

Cancer · Stroke · Tissue plasminogen activator · Ischemic stroke · Intracerebral

hemorrhage · Hypercoagulability · Arterial embolism · Venous thromboembolism

Introduction

Compromised blood flow in arteries or veins can lead to impaired oxygen delivery to the central nervous system and result in irreversible tissue injury causing a stroke. Such injury can occur as a result of blood clots (ischemic strokes) or due to rupture of blood vessels leading to hemorrhage and secondary tissue injury (hemorrhagic strokes). Overall, stroke is the fifth leading cause of death in the United States, with an incidence of about 800,000 new cases annually and a high societal cost burden [27, 40].

Despite being a distinct clinical entity in itself, stroke is frequently the initial presenting “symptom” of cancer and thus the first expression of an underlying but unknown cancer state [39]. Ischemic strokes occur in a large number of cancer patients and can be both symptomatic and asymptomatic (silent infarctions). Hemorrhagic strokes have a higher association with hematological malignancies and lung cancer. In patients with leukemia and lymphoma, 72% and 36% of strokes, respectively, have found to be hemorrhagic. Other associated hematological abnormalities like chemotherapy-induced thrombocytopenia, disseminated intravascular coagulopathy (DIC), and other coagulation disorders also contribute to the risk of hemorrhagic strokes [46].

Epidemiology

Compared to the general population, patients with cancer have a higher prevalence of stroke, with an annual incidence up to 7% for ischemic strokes and a lifetime probability of occurrence of 50% [16]. 0.5–4.5% of all patients with ischemic strokes and up to 5% of those with strokes of undermined causes (cryptogenic strokes) are diagnosed of an unknown malignancy during hospitalization [39].

Stroke can be the initial clinical manifestation of an occult cancer state, with a majority being

diagnosed during the first 6 months of follow-up after stroke [7, 16]. Ischemic strokes in cancer and non-cancer patients are mediated by similar risk factors such as older age, smoking, obesity, physical inactivity, hypertension, diabetes, hypercholesterolemia, and certain cardiac conditions like atrial fibrillation. Although the prevalence of various ischemic stroke mechanisms (mainly thromboembolism due to atherosclerosis, cardioembolism, and small vessel disease) is similar between patients with and without cancer, the traditional stroke mechanisms attributable to these specific risk factors are absent in up to 40% of patients with cancer [5].

Etiology

First described by Trousseau in 1865, hypercoagulability has been proposed as a central mechanism of ischemic strokes in patients with cancer. The risk of thrombosis in patients with cancer is an aggregate of individual vascular risk factors as described above, the type of cancer itself and the secondary effects of the cancer (non-bacterial thrombotic endocarditis leading to cardiac embolism, local compressive effects) and its treatment. Adenocarcinomas have been shown to have the greatest thrombotic risk overall [39] with high prevalence of prothrombotic states being associated with lung, prostate, colorectal, breast, gynecological cancers and lymphoma [41].

Patients with cancer-associated strokes have also been found to have lower body mass index and lower levels of hemoglobin, albumin, and triglycerides compared to non-cancer strokes, with higher levels of coagulation parameters such as prothrombin time (PT), international normalized ratio (INR), and D-dimer and fibrinogen levels [25, 47].

Pathophysiology

Cancer-associated ischemic strokes have several mechanisms that lead to hypercoagulability. These include derangements of the coagulation

cascade, tumor mucin secretion, paraneoplastic effects, and a prothrombotic, inflammatory, vascular endothelium as a result of necrotizing factor and interleukins leading to the formation of fibrin- and platelet-rich thrombi in the vasculature or along normal heart valves that can embolize (non-bacterial, marantic endocarditis) [7, 15, 16, 33].

Solid and nonsolid tumors and the consequences of treatment also affect the mechanisms by which strokes occur. These effects occur as a result of (1) direct tumor effects, such as occlusive disease leading to thrombo-emboli, local compression of blood vessels, or meningeal extension of tumors, (2) consequences of medical complications of cancer such as coagulopathy and underlying infections (especially fungal), or (3) treatment related, such as chemotherapy-related thrombocytopenia, hypercoagulability, or radiation-induced accelerated atherosclerosis, leading to hemorrhagic strokes [11, 33]. Common chemotherapeutic agents that are associated with high incidence of strokes include newer anti-angiogenic agents such as bevacuzimab, along with cisplatin-based chemotherapy, cyclophosphamide, 5-fluorouracil Taxol paclitaxel, L-asparaginase, and tamoxifen [45, 46] due to both systemic effects of the chemotherapy and direct effects on the coagulation cascade causing changes in platelet aggregation, increased levels of von Willebrand factor (cisplatin), and lower levels of anti-thrombin III and possibly protein C (tamoxifen). Complications of bone marrow transplantation can also cause thrombocytopenia and increased risk for hemorrhagic strokes.

Chemotherapeutic agents can also lead to posterior reversible encephalopathy syndrome (PRES), which consists of stroke-like symptoms, headache, disturbance of consciousness, seizures, and visual symptoms. Although associated with other etiologies such as malignant hypertension, eclampsia, renal failure, autoimmune conditions, and general anesthesia, there is a significant association of PRES and immunosuppressive therapies. The time interval between the last chemotherapy and first symptoms varies from a few hours after treatment to 5 weeks posttreatment and can occur within the first three cycles of

chemotherapy. Proposed mechanisms by which immunosuppressive and cytotoxic agents cause PRES include endothelial injury and altered cerebral autoregulation that leads to breakdown of the blood-brain barrier and subsequent brain edema [6]. Specific antineoplastic agents like pemetrexed, methotrexate, vincristine, ifosfamide, cyclosporine, fludarabine, cytarabine, 5-fluorouracil, gemcitabine, and cisplatin have been associated with this condition, along with high-dose, multidrug chemotherapy, erythropoietin, and autologous stem cell transplants [43, 44]. Although PRES is a potentially reversible condition with supportive care and medical management that includes treatment of seizures, gradual reduction of blood pressure and removal of the offending agent(s), recurrences have been reported in 6% of cases and death in up to 15% of patients [22].

Cancer can also result in a vasculopathy involving the veins or arteries in various ways. Solid tumors can often cause venous infarctions by either exerting local mass effect or compression of venous sinuses or can proliferate along venous structures adjacent to the dura invading the sinuses leading to compromised venous drainage resulting in congestion and swelling causing hemorrhagic venous infarctions. Tumors can also spread into the leptomeningeal or Virchow Robin spaces and encompass the penetrating arteries, leading to vascular congestion and inflammation leading to vasculitis and compromise of cerebral blood flow (cerebral vasospasm). Commonly associated tumors with this process include lymphomas and primary lung cancer with lung metastases, where a tumor enters the pulmonary circulation and is distributed by arterial blood flow. Alternatively, intracardiac metastases or primary tumors such as myxomas can directly embolize to the cerebral circulation [33].

Cancer patients have up to a sevenfold increased risk of developing venous thromboembolism compared with those without cancer [8, 13]. This underlying hypercoagulability state predisposes cancer patients to developing deep venous thrombi in the pelvic and/or lower extremity venous system that can lead to arterial strokes by the migration of the these thrombi to the heart

that can paradoxically embolize to the arterial system via a right-to-left shunt as a result of a patent foramen ovale [14, 48]. While there are no studies to-date directly linking immunotherapy to stroke, it can be associated with a higher risk of venous thromboembolism.

Tumor cells can also invade the walls of the intracranial vasculature, leading to aneurysm formation that are typically located in the distal vasculature and can result in parenchymal or sub-arachnoid hemorrhage [28]. The diagnosis is typically challenging and is made at autopsy or by observing growth of metastases at sites of previous infarction on neuroimaging scans. Patients with certain types of leukemia such as acute myelogenous leukemia and elevated leukocyte counts ($>100,000/\text{mm}^3$) can develop intravascular leukostasis leading to infarction that is usually hemorrhagic [33].

Surgical procedures and radiotherapy related to cancer treatments also confer an increased stroke risk, with up to 60% of ischemic strokes occurring in the post-operative period after resection of an intracranial neoplasm. Patients undergoing radical neck dissection for head and neck malignancies are at operative risk for infarction after ligation of the common carotid artery. There is also a delayed risk of stroke (twofold risk at about 5 years after a median radiation dose of 64 Gy) subsequent to irradiation of the head or neck, which can induce accelerated atherosclerosis [18] and an increased rate of carotid stenosis of greater than 70% in patients receiving an equivalent dose of radiotherapy (up to 66 Gy) to the neck [10, 33].

Clinical Features

The initial priority in the care of a stroke patient is similar to that of any potentially critically ill patient: stabilization of the airway, breathing, circulation (ABCs), followed by an assessment of neurological symptoms and medical comorbidities. The overall goal is not only to identify patients with possible strokes but also to exclude conditions that often present with stroke-like symptoms, such as hypoglycemia and migraines.

Common symptoms attributable to strokes include focal neurologic deficits such as sudden impairment in speech production or quality, vision, strength or sensation (variably affecting the face, arm, and leg), gait, and/or coordination. Subtle manifestations include cognitive dysfunction, reduced comprehension of language, and loss of fine motor skills [21]. Brain tumors or metastases can also have a stroke-like presentation as a consequence of lesion-induced seizures or acute hemorrhage into the tumor itself [33].

Diagnosis

The most crucial element in the history is the time of symptom onset or the last time the patient was at “normal” baseline state of health. A time window of 0–4.5 h from symptom onset/last seen normal is one of the main inclusion criteria for ischemic stroke patients to be able to receive fibrinolytic treatment. Other relevant history includes the time course and nature of symptoms, evaluation of risk factors for arteriosclerosis and cardiac disease, history of central nervous system cancer, anticoagulation or chemotherapy use, thrombocytopenia, drug abuse, migraine, seizure, infection, trauma, or pregnancy. Since the benefits of treatment with fibrinolytic therapy are time dependent, with faster treatment times resulting in better outcomes, the initial neurological examination consists of a standardized neurological assessment known as the National Institutes of Health Stroke Scale (Table 1) to ensure that the major components of a neurological examination are performed in a timely and uniform manner. Other tests that are emergently performed include a non-contrast head computed tomography (CT) scan to exclude any intracranial hemorrhage, blood glucose check, complete blood count with platelet count and PT, INR, and activated partial thromboplastin time (aPTT) if thrombocytopenia or coagulopathy is suspected, especially for patients on chemotherapy. Fibrinolytic therapy is not delayed however while awaiting the results of the PT, aPTT, or platelet count unless a bleeding abnormality or thrombocytopenia is suspected, the patient has been taking warfarin and heparin

Table 1 National Institutes of Health Stroke Scale (NIHSS)

Item	Title	Response/score
1A	Level of consciousness	0 – Alert 1 – Drowsy 2 – Obtunded 3 – Coma/unresponsive
1B	Orientation questions (2)	0 – Answers both correctly 1 – Answers 1 correctly 2 – Answers neither correctly
1C	Response to commands (2)	0 – Performs both tasks correctly 1 – Performs 1 task correctly 2 – Performs neither
2	Gaze	0 – Normal horizontal movements 1 – Partial gaze palsy 2 – Complete gaze palsy
3	Visual fields	0 – No visual field defect 1 – Partial hemianopia 2 – Complete hemianopia 3 – Bilateral hemianopia
4	Facial movement	0 – Normal 1 – Minor facial weakness 2 – Partial facial weakness 3 – Complete unilateral palsy
5	Motor function (arm) a. Left b. Right	0 – No drift 1 – Drift before 10 s 2 – Falls before 10 s 3 – No effort against gravity 4 – No movement
6	Motor function (leg) a. Left b. Right	0 – No drift 1 – Drift before 5 s 2 – Falls before 5 s 3 – No effort against gravity 4 – No movement
7	Limb ataxia	0 – No ataxia 1 – Ataxia in 1 limb 2 – Ataxia in 2 limbs
8	Sensory	0 – No sensory loss 1 – Mild sensory loss 2 – Severe sensory loss
9	Language	0 – Normal 1 – Mild aphasia 2 – Severe aphasia 3 – Mute or global aphasia
10	Articulation	0 – Normal 1 – Mild dysarthria 2 – Severe dysarthria
11	Extinction or inattention	0 – Absent 1 – Mild loss (1 sensory modality lost) 2 – Severe loss (2 modalities lost)

Source: National Institute of Neurological Disorders and Stroke. Available for download at: https://www.ninds.nih.gov/sites/default/files/NIH_Stroke_Scale.pdf

and is on chemotherapy, or anticoagulation use is uncertain. All acute stroke patients undergo cardiovascular evaluation with an admission

electrocardiogram and telemetry monitoring after admission to the hospital, both for determination of the cause of the stroke and to optimize

immediate and long-term management. Although atrial fibrillation may be evident on an admission electrocardiogram, its absence does not exclude its etiology as the cause of the event and thus warrants telemetry monitoring during the hospitalization and/or long-term monitoring after discharge.

Acute neuroimaging in stroke generally involves an initial non-iodinated contrast head CT scan to identify any acute intracranial hemorrhage and should be obtained within 25 min of the patient's arrival to the emergency department (ED) [21]. Other signs of early ischemia on a CT scan such as a hyperdense artery, loss of gray-white matter differentiation, sulcal effacement suggestive of early edema, and loss of the architecture of the deep gray nuclei corroborate the diagnosis of stroke but do not preclude treatment with fibrinolytic therapy [35]. For patients who have malignancies that have a high predilection for brain metastasis, a contrast-enhanced CT or magnetic resonance imaging (MRI) scan can be considered prior to tPA administration to ensure lack of parenchymal brain disease that could increase the risk of hemorrhage. Helical CT angiography (CTA) provides a means to rapidly and noninvasively evaluate the intracranial and extracranial vasculature in acute, subacute, and chronic stroke settings and provides important information about the presence of significant arterial vessel occlusions or stenosis that can be used in the acute stroke scenario to determine further endovascular treatment options in selected patients with large artery occlusions within 6 h of symptom onset [21]. Brain perfusion imaging using CT or MRI provides information about brain tissue undergoing ischemia but is not irreversibly infarcted, providing quantification of the ischemic penumbra. Combined with parenchymal (non-contrast CT or MRI) and vascular imaging (CTA or MR angiography), perfusion CT or MRI can be used to select certain stroke patients with large vessel occlusions in the intracranial internal or middle cerebral arteries for mechanical thrombectomy and clot extraction using cerebral angiography within 6–24 h from symptom onset/last seen normal time [1, 34].

Standard MRI sequences used to diagnose acute ischemic stroke include diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences that are the most sensitive and specific imaging technique for acute infarction, with DWI having a high sensitivity (88–100%) and specificity (95–100%) for detecting infarcted within minutes of symptom onset. DWI/ADC sequences also allow for identification of the lesion size, site, and age, along with detection of relatively small cortical lesions and small deep or subcortical lesions (especially those in the brain stem or cerebellum) that can be poorly identifiable on a non-contrast head CT scan. Other MRI sequences such as T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR) are relatively insensitive to the changes of acute ischemia within the first hours, although they can be useful in identifying areas of infarcted that are more than 4.5 h [49] and provide estimates of the age of hemorrhage in relation to the initial occurrence [9, 21]. Patients with ischemic strokes and associated cancer have a higher prevalence of diffuse strokes that are generally multifocal, spanning different brain areas and cerebrovascular territories [5, 25, 39, 47].

An acutely hemorrhagic brain tumor lesion can be challenging to distinguish from a hemorrhagic stroke due to other more conventional causes, such as small vessel hypertensive lipohyalinosis or amyloid angiopathy. However, brain tumor hemorrhage is generally lobar (which is unusual for hypertension-associated hemorrhage) or located in an atypical location such as the corpus callosum, usually associated with marked edema surrounding the clot due to the underlying tumor, and can be associated with a ringlike, high-density area corresponding to the blood around a low-density center resulting from bleeding by tumor vessels at the junction of tumor and adjacent brain parenchyma [23]. Renal, thyroid, and germ cell carcinoma brain metastases, as well as melanoma, have the greatest tendency to be hemorrhagic, although brain metastases from lung cancer (bronchogenic carcinoma) are the most common cause [33]. The majority of underlying hemorrhagic primary brain tumors are malignant (i.e., high-grade gliomas), although

meningiomas, oligodendrogliomas, and pituitary adenomas are also prone to hemorrhage. The most common primary brain neoplasms that bleed spontaneously are glioblastoma multiforme (GBM) and malignant astrocytoma. Less common tumors that cause parenchymal hemorrhage (but can cause primary intraventricular hemorrhage) are ependymoma, subependymoma, choroid plexus papilloma, intraventricular meningioma, neurocytoma, granular cell tumor, metastases, craniopharyngioma, and pituitary tumors that erode through the floor of the third ventricle [26].

Management

Pharmacologic

Administration of intravenous fibrinolytic therapy with tissue plasminogen activator (tPA) within 4.5 h of a suspected ischemic stroke is the standard of care and is associated with an increase in the odds of a favorable outcome [17, 50, 51]. The major risk of intravenous tPA treatment remains symptomatic intracranial hemorrhage with the initial evaluation focused toward screening patients with standard inclusion/exclusion criteria for tPA (Table 2). Since the benefit of therapy is time dependent, treatment should be initiated as soon as possible, targeting a door-to-bolus time of 60 min from hospital arrival. Standard dosing for tPA is 0.9 mg/kg (maximum dose 90 mg) with 10% of the dose given as a bolus over 1 min and the remainder as an infusion over an hour. Mechanical clot extraction via cerebral angiography can be performed at advanced stroke centers for a subgroup of stroke patients who are either ineligible for treatment with intravenous tPA or who receive tPA and have a concurrent large artery vessel occlusion in the internal or middle cerebral arteries and are within the first 6 h of symptom onset (Table 3). For other selected patients who present within 6–24 h from stroke-symptom onset, mechanical thrombectomy might also be considered, depending on specific clinical and neuroimaging (perfusion imaging) criteria [37, 38].

Besides coagulopathy and active hemorrhage, the most significant exclusion for intravenous tPA for cancer patients includes intracranial neoplasms, which can be divided into extra-axial and intra-axial tumors. Risks of intravenous tPA should thus be based on the anatomic and histological factors of a particular neoplasm if possible. Although data on intravenous tPA in the setting of intracranial neoplasms are confined to case reports, systemic thrombolysis appears safe in extra-axial, intracranial neoplasms, such as meningiomas. The same is not however applicable to intra-axial neoplasms such as intracranial metastases and primary brain neoplasms such as GBMs, and thus tPA should be avoided in cases where an intra-axial brain parenchymal tumor is suspected due to the risk of hemorrhage. Ultimately, the histology, location, and baseline bleeding risk of the tumor can inform reasonable intravenous tPA administration in these patients [12]. Such patients can alternatively be screened for potential mechanical thrombectomy based on current guidelines, especially if they are functionally independent and have a favorable prognosis and life expectancy given their underlying cancer and ongoing treatment course. A general history of cancer or active systemic malignancy (without brain or spinal cord metastases) should also not necessarily prevent stroke patients from receiving treatment with intravenous tPA (assuming other inclusion/exclusion criteria are met), although the risks and benefits must be carefully assessed, discussed with the patient/family, and considered with other medical providers involved in the oncologic care of the patient.

Subsequent care of the stroke patient after management in the ED largely depends on risk factor modification and investigation of the underlying etiology for the stroke. Oral administration of aspirin (initial dose 325 mg) within 24–48 h after stroke onset is recommended for treatment of most patients, depending on whether tPA is administered and consideration of the immediate bleeding risk. Patients who have elevated blood pressure on initial arrival and are otherwise eligible for treatment with intravenous tPA should have their blood pressure carefully lowered so that their systolic blood pressure is <185 mmHg

Table 2 Inclusion and exclusion criteria for treatment with intravenous tPA

Inclusions	Diagnosis of ischemic stroke causing measurable neurological deficits
	Aged ≥ 18 years
	Onset of symptoms/last known well 0–4.5 ^a h before beginning treatment
Exclusions	CT brain with acute intracranial hemorrhage
	Severe head trauma or prior stroke in previous 3 months
	Arterial puncture at a non-compressible site in previous 7 days
	History of significant previous intracranial hemorrhage
	Intra-axial neoplasm, arteriovenous malformation, or aneurysm (safe if size <10 mm, unruptured and unsecured)
	Recent intracranial or intraspinal surgery within prior 3 months
	Persistently elevated blood pressure (systolic >185 mmHg or diastolic >110 mmHg) intractable to medical therapy
	Symptoms known or suspected to be associated with aortic arch dissection
	Active internal bleeding
	Platelet count <100,000/mm
	Heparin received within 48 h, resulting in abnormally elevated aPTT greater than the upper limit of normal
	Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
	Treatment dose of LMWH within previous 24 h
	Symptoms consistent with infective endocarditis
	Current use of anticoagulant with INR >1.7, aPTT >40 s or PT >15 s
	Blood glucose concentration <50 mg/dL (2.7 mmol/L)
	CT demonstrates multi-lobar infarction (hypodensity >1/3 cerebral hemisphere)
Exclusions (relative)	Minor or rapidly improving stroke symptoms (potential disability of symptoms should be considered)
	Pregnancy (risks vs. benefits of tPA should be considered)
	Seizure at onset with postictal residual neurological impairments attributable to the seizure
	Major surgery or serious trauma within previous 14 days
	Significant gastrointestinal or urinary tract hemorrhage (within previous 21 days)
	Severe stroke (NIHSS>25) ^a
	Taking an oral anticoagulant regardless of INR ^a
	History of both diabetes and prior ischemic stroke ^a

Source: Refs. [21, 38]

aPTT activated partial thromboplastin time, CT computed tomography, ECT ecarin clotting time, INR international normalized ratio, PT partial thromboplastin time, LMWH low molecular weight heparin, tPA tissue plasminogen activator, TT thrombin time, NIHSS National Institutes of Health Stroke Scale

^aRelative exclusions for treatment between 3 and 4.5 h from symptom onset/last known well time

and their diastolic blood pressure is <110 mmHg prior to tPA administration and <180/105 after tPA for the first 24 h. Beyond that, blood pressure goals and medications are initiated depending on the patient’s neurologic and medical comorbidities based on optimizing cerebral perfusion in ischemic stroke or minimizing the risk of hematoma expansion in cases of hemorrhagic stroke. For patients with hemorrhagic strokes, systolic blood pressure is lowered to a goal of systolic of 140 for the first 24 h or beyond depending

on the patient’s clinical condition. Medications such as fresh frozen plasma, three- or four-factor prothrombin complex concentrate (PCC), or idarucizumab [36] can be used to acutely reverse the anticoagulation effects of warfarin or dabigatran, respectively, and are administered depending on the INR level and administration of last dose. Pharmacotherapy for management of diabetes and hypercholesterolemia is also initiated. Anticoagulation is generally initiated for prevention of venous thromboembolism within

Table 3 Evidence-based criteria for endovascular therapy with stent retrievers

(a) Pre-stroke mRS score 0–1
(b) Vascular occlusion of the ICA or proximal MCA (M1 segment) artery
(c) Age ≥ 18 years
(d) NIHSS score ≥ 6
(e) ASPECTS ≥ 6
(f) Treatment can be initiated (groin puncture) within 6 h of symptom onset/last known well time
(g) The use of endovascular therapy with stent retrievers can be considered on a case-by-case basis for causative occlusions of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries
(h) Observation of patients after intravenous tPA to assess for clinical response before pursuing endovascular therapy is not required
<i>Additional criteria for 6–24 h from symptom onset/last known well time</i>
(a) In selected patients with acute ischemic stroke within 6–16 h of last known normal who have a LVO in the anterior circulation and meet DAWN ^a or DEFUSE 3 ^b trials' inclusion/exclusion criteria, mechanical thrombectomy is recommended
(b) In selected patients with AIS within 6–24 h of last known normal who have LVO in the anterior circulation and meet other DAWN ^a trial inclusion/exclusion criteria, mechanical thrombectomy is reasonable

Source: Refs. [37, 38]

mRS modified Rankin scale, tPA tissue plasminogen activator, ICA internal carotid artery, MCA middle cerebral artery, NIHSS National Institutes of Health Stroke Scale, ASPECTS Alberta stroke program early CT score, LVO large vessel occlusion, CT computed tomography, MRI magnetic resonance imaging, DWI diffusion-weighted imaging

^aInclusions [34] = Pre-stroke mRS score 0–1; persistent occlusion >60 min after tPA administration; contraindications for tPA; NIHSS ≥ 10 ; clinical imaging mismatch [0–20 ml core infarct, NIHSS ≥ 10 if age ≥ 80 ; 0–30 ml core infarct, NIHSS ≥ 10 for age < 80; 31 ml to <50 ml core infarct, NIHSS ≥ 20 for age < 80]

^bInclusions [1] = Pre-stroke mRS score 0–2; Age 18–85; NIHSS ≥ 6 ; target mismatch profile on CT perfusion or MRI (ischemic core volume is <70 ml, mismatch ratio > 1.8, and mismatch volume > 15 ml or DWI lesion volume < 25 ml)

24–48 h, depending on clinical variables that might increase the risk of hemorrhage.

Atrial fibrillation is a well-known risk factor for ischemic stroke in cancer and non-cancer patients and generally warrants anticoagulation based on risk stratification scores and bleeding risks. Patients categorized as low risk are not routinely recommended anticoagulation prophylaxis. Cancer is known to increase the risk of ischemic stroke, but it is not clear to what extent cancer is a risk factor of ischemic stroke in patients with atrial fibrillation with a low stroke risk score. Cancer diagnosis within 1 year increases the risk of stroke in atrial fibrillation patients with low stroke risk score, particularly in patients greater than 65 years of age. These patients may thus benefit from anticoagulation treatment to lower the risk of ischemic stroke [3].

Patients with major ischemic infarctions are at high risk for brain edema and increased intracranial pressure, which are associated with major morbidity and mortality.

Medical management for cerebral edema includes hyperosmolar therapy and supportive

care in a neuroscience intensive care unit with neuro-critical care and neurosurgical expertise in caring for such patients along with close monitoring for neurological deterioration. For selected patients based on age, medical comorbidities, and patient/family expectations for favorable outcomes, decompressive surgical evacuation of a space-occupying cerebellar infarction is effective in preventing and treating herniation and brain stem compression, as is decompressive surgery for malignant edema of the cerebral hemisphere in providing a life-saving benefit [52]. Placement of an external ventricular drain can be useful in patients with acute hydrocephalus secondary to ischemic stroke or intraventricular hemorrhage [19, 21]. For patients with occlusions of the major venous sinuses and associated venous infarctions, recanalization of a sinus is less likely to be achieved by conventional treatment with anticoagulation and can necessitate definitive therapy of the occluding tumor, usually with radiation [33]. Although there is no clear benefit of anticoagulation in the absence of a sinus thrombosis or venous thromboembolism, cancer

patients with ischemic strokes attributable to cancer-related hypercoagulability are often anticoagulated given the high risk of stroke recurrence (unless there is an excessive risk of systemic bleeding related to their cancer) [20, 32].

Non-pharmacologic

Cardiac monitoring is performed for at least the first 24 h to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that can necessitate emergency cardiac interventions. Airway support is often needed for patients who have decreased consciousness or bulbar dysfunction. Supplemental oxygen should be provided to maintain oxygen saturation >94%. Sources of hyperthermia (temperature >38 °C) should be identified and treated, and antipyretic medications should be administered to lower temperature. In patients with elevated blood pressure who do not receive fibrinolysis, guidelines recommend permissive hypertension to promote cerebral perfusion and to only treat the blood pressure if the systolic blood pressure is >220 mmHg and diastolic blood pressure is >120 mmHg, unless there is concern for end-organ damage. Hypovolemia should be avoided, along with hypoglycemia (blood glucose <60 mg/dL) or hyperglycemia (>180 mg/dL). Appropriate antibiotics should be used for treatment of pneumonia, urinary tract infections, or other concurrent infections that can contribute to morbidity. Assessment of swallowing before the patient begins eating, drinking, or receiving oral medications is important, along with early mobilization with physical and occupational therapy for less severely affected stroke patients. The use of intermittent external compression devices is vital for treatment of patients who cannot receive anticoagulants for prevention of venous thromboembolism.

Prognosis

Cancer patients are at an increased risk of stroke, especially within 1 year of cancer diagnosis [33]. For ischemic stroke patients diagnosed with cancer

within 6 months (~1.0%), it is likely that they already had an underlying, pre-existing malignancy at the time of stroke onset [41]. Patients newly diagnosed with common solid or hematologic cancers face a considerably increased short-term risk of arterial thromboembolism [31]. Advanced cancer stage, which is directly related to the overall tumor burden and extent of disease, is associated with increased stroke risk and carries a poor prognosis for survival, with a three-fold increased risk for death [31].

D-dimer is a marker for hypercoagulability, with increased D-dimer levels being associated with increased tumor burden and stage. Elevated D-dimer levels, however, have been associated with ischemic stroke in both cancer- and non-cancer-associated strokes. Some studies have found higher D-dimer levels to be associated with more widespread distribution of ischemic strokes across multiple vascular territories in cancer patients compared to non-cancer patients [5]. Along with high D-dimer levels, systemic metastases and diabetes are independent predictors of poor survival in cancer patients with cryptogenic strokes [4, 42, 45].

Patients with acute ischemic stroke in the setting of active cancer (especially adenocarcinoma) face a substantial short-term risk of recurrent ischemic stroke with cumulative rates of recurrent events being reported up to 7%, 13%, and 16% at 1, 3, and 6 months, respectively [29]. The stroke recurrence among cancer-related strokes was found to be associated with unconventional stroke etiologies, the absence of cancer treatment, extracranial stenosis, and cerebral microbleed numbers [25]. Other biomarkers such as erythrocyte sedimentation rate, high-sensitivity C-reactive protein, fibrinogen, and pro-b-type natriuretic peptide have also been shown to be higher in cancer patients with ischemic stroke compared with non-cancer patients and are associated with an increased frequency of large artery atherosclerosis as a potential etiology for ischemic strokes in cancer patients [24].

The increased risk of thrombosis in cancer patients also tends to correlate well with advanced stage of disease, increased tumor volume, and prolonged hospitalization [13]. The presence of

venous thromboembolism (without any associated stroke) in patients with cancer is an independent predictor of poor survival in these patients [2].

Survival can be limited in patients with active systemic cancer who have a cryptogenic ischemic stroke independent of several potential confounders, such as age, functional status, presence of systemic metastases, and adenocarcinoma histology. The association of cryptogenic stroke with death is even stronger in patients with radiographic cardioembolic infarction patterns. In fact, only 17% of patients with cryptogenic stroke and 9% of those with radiographic cardioembolic infarction patterns survived to 1 year in one study. This is in contrast to the general stroke population, where cryptogenic strokes are typically associated with lower mortality and recurrence than strokes from known mechanisms [30].

Conclusion

The prognosis for patients with cancer and stroke is complex and is dependent on a multitude of variables related to a patient's conventional risk factors for stroke, type and stage of cancer, treatment course, and the nature and disability burden of the stroke. Although the outcome is poor for patients with systemic cancer, the survival rate is increasing with the development of more effective cancer treatments [11].

References

- Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–18. <https://doi.org/10.1056/nejmoa1713973>.
- Amer M. Cancer-associated thrombosis: clinical presentation and survival. *Cancer Manag Res*. 2013; 5: 165. <https://doi.org/10.2147/cmar.s47094>.
- Atterman A, Gigante B, Asplund K, et al. Cancer diagnosis as a risk factor of ischemic stroke in atrial fibrillation patients with low stroke risk score. *Thromb Res*. 2018;164:S209. <https://doi.org/10.1016/j.thromres.2018.02.064>.
- Ay C, Dunkler D, Pirker R, et al. High D-dimer levels are associated with poor prognosis in cancer patients. *Haematologica*. 2012;97:1158–64. <https://doi.org/10.3324/haematol.2011.054718>.
- Bang OY, Seok JM, Kim SG, et al. Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. *J Clin Neurol*. 2011;7:53. <https://doi.org/10.3988/jcn.2011.7.2.53>.
- Bartynski W. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. *Am J Neuroradiol*. 2008;29:1043–9. <https://doi.org/10.3174/ajnr.a0929>.
- Bick RL. Cancer-associated thrombosis. *N Engl J Med*. 2003;349:109–11. <https://doi.org/10.1056/nejmp030086>.
- Blom JW. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA*. 2005;293:715. <https://doi.org/10.1001/jama.293.6.715>.
- Bradley WG. MR appearance of hemorrhage in the brain. *Radiology*. 1993;189:15–26. <https://doi.org/10.1148/radiology.189.1.8372185>.
- Cheng SW, Wu LL, Ting AC, et al. Irradiation-induced extracranial carotid stenosis in patients with head and neck malignancies. *Am J Surg*. 1999;178:323–8. [https://doi.org/10.1016/s0002-9610\(99\)00184-1](https://doi.org/10.1016/s0002-9610(99)00184-1).
- Cocho D, Gendre J, Boltes A, et al. Predictors of occult cancer in acute ischemic stroke patients. *J Stroke Cerebrovasc Dis*. 2015;24:1324–8. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2015.02.006>.
- Demaerschalk BM, Kleindorfer DO, Adeoye OM, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke. *Stroke*. 2015;47:581–641. <https://doi.org/10.1161/str.0000000000000086>.
- Donati MB, Falanga A. Pathogenetic mechanisms of thrombosis in malignancy. *Acta Haematol*. 2001; 106:18–24. <https://doi.org/10.1159/000046585>.
- Gemmete JJ, Pandey AS, Chaudhary N, et al. Paradoxical embolus to the brain from embolization of a carotid body tumor. *J Neurointerv Surg*. 2011;4:e12.
- Gonzalez-Quintela A, Candela M, Vidal C, et al. Non-bacterial thrombotic endocarditis in cancer patients. *Acta Cardiol*. 1991;46:1–9.
- Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. *Medicine*. 1985;64:16–35. <https://doi.org/10.1097/00005792-198501000-00002>.
- Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–29. <https://doi.org/10.1056/nejmoa0804656>.
- Haynes JC, Machtay M, Weber RS, et al. Relative risk of stroke in head and neck carcinoma patients treated with external cervical irradiation. *Laryngoscope*. 2002;112:1883–7. <https://doi.org/10.1097/00005537-200210000-00034>.
- Hemphill JC, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage. *Stroke*. 2015;46:2032–60. <https://doi.org/10.1161/str.0000000000000069>.
- Jang H, Lee JJ, Lee MJ, et al. Comparison of enoxaparin and warfarin for secondary prevention of cancer-associated stroke. *J Oncol*. 2015;2015:1–6. <https://doi.org/10.1155/2015/502089>.

21. Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947. <https://doi.org/10.1161/str.0b013e318284056a>.
22. Kabre R, Kamble K. Gemcitabine and Cisplatin induced posterior reversible encephalopathy syndrome: a case report with review of literature. *J Res Pharm Pract*. 2016;5:297. <https://doi.org/10.4103/2279-042x.192464>.
23. Kase CS. Intracerebral hemorrhage: non-hypertensive causes. *Stroke*. 1986;17:590–5. <https://doi.org/10.1161/01.str.17.4.590>.
24. Kim K, Lee J-H. Risk factors and biomarkers of ischemic stroke in cancer patients. *J Stroke*. 2014;16:91. <https://doi.org/10.5853/jos.2014.16.2.91>.
25. Kim J-M, Jung K-H, Park KH, et al. Clinical manifestation of cancer related stroke: retrospective case-control study. *J Neurooncol*. 2013;111:295–301. <https://doi.org/10.1007/s11060-012-1011-4>.
26. Mohr JP. *Stroke: pathophysiology, diagnosis, and management*. Philadelphia: Elsevier/Saunders; 2011.
27. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics – 2016 update. *Circulation*. 2015;133:e38. <https://doi.org/10.1161/cir.0000000000000350>.
28. Murata J-I, Sawamura Y, Takahashi A, et al. Intracerebral hemorrhage caused by a neoplastic aneurysm from small-cell lung carcinoma. *Neurosurgery*. 1993;32:124–6. <https://doi.org/10.1227/00006123-199301000-00019>.
29. Navi BB, Singer S, Merkler AE, et al. Recurrent thromboembolic events after ischemic stroke in patients with cancer. *Neurology*. 2014a;83:26–33. <https://doi.org/10.1212/wnl.0000000000000539>.
30. Navi BB, Singer S, Merkler AE, et al. Cryptogenic subtype predicts reduced survival among cancer patients with ischemic stroke. *Stroke*. 2014b;45:2292–7. <https://doi.org/10.1161/strokeaha.114.005784>.
31. Navi BB, Reiner AS, Kamel H, et al. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol*. 2017;70:926–38. <https://doi.org/10.1016/j.jacc.2017.06.047>.
32. Navi BB, Marshall RS, Bobrow D, et al. Enoxaparin vs aspirin in patients with cancer and ischemic stroke. *JAMA Neurol*. 2018;75:379. <https://doi.org/10.1001/jamaneurol.2017.4211>.
33. Nguyen T, DeAngelis LM. Stroke in cancer patients. *Curr Neurol Neurosci Rep*. 2006;6:187–92. <https://doi.org/10.1007/s11910-006-0004-0>.
34. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21. <https://doi.org/10.1056/nejmoa1706442>.
35. Patel SC, Levine SR, Tilley BC, et al. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA*. 2001;286:2830–8. <https://doi.org/10.1001/jama.286.22.2830>.
36. Pollack CV, Reilly PA, Ryn JV, et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med*. 2017;377:431–41. <https://doi.org/10.1056/nejmoa1707278>.
37. Powers WJ, Derdeyn CP, Biller J, et al. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment. *Stroke*. 2015;46:3020–35. <https://doi.org/10.1161/str.0000000000000074>.
38. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e46. <https://doi.org/10.1161/str.0000000000000158>.
39. Quintas S, Rogado J, Gullón P, et al. Predictors of unknown cancer in patients with ischemic stroke. *J Neurooncol*. 2018;137:551–7. <https://doi.org/10.1007/s11060-017-2741-0>.
40. Rha J-H, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke*. 2007;38:967–73. <https://doi.org/10.1161/01.str.0000258112.14918.24>.
41. Selvik HA, Thomassen L, Bjerkreim AT, et al. Cancer-associated stroke: the Bergen NORSTROKE study. *Cerebrovasc Dis Extra*. 2015;5:107–13. <https://doi.org/10.1159/000440730>.
42. Shin Y-W, Lee S-T, Jung K-H, et al. Predictors of survival for patients with cancer after cryptogenic stroke. *J Neurooncol*. 2016;128:277–84. <https://doi.org/10.1007/s11060-016-2106-0>.
43. Sioka C, Kyritsis AP. Central and peripheral nervous system toxicity of common chemotherapeutic agents. *Cancer Chemother Pharmacol*. 2008;63:761–7.
44. Smets G-J, Loyson T, Paesschen WV, et al. Posterior reversible encephalopathy syndrome possibly induced by pemetrexed maintenance therapy for lung cancer: a case report and literature review. *Acta Clin Belg*. 2017;1–7. <https://doi.org/10.1080/17843286.2017.1403103>.
45. Sorgun MH, Kuzu M, Ozer IS, et al. Risk factors, biomarkers, etiology, outcome and prognosis of ischemic stroke in cancer patients. *Asian Pac J Cancer Prev*. 2018;19:649–53.
46. Stefan O, Vera N, Otto B, et al. Stroke in cancer patients: a risk factor analysis. *J Neurooncol*. 2009;94:221–6. <https://doi.org/10.1007/s11060-009-9818-3>.
47. Sun B, Fan S, Li Z, et al. Clinical and neuroimaging features of acute ischemic stroke in cancer patients. *Eur Neurol*. 2016;75:292–9. <https://doi.org/10.1159/000447126>.
48. Thaler DE, Saver JL. Cryptogenic stroke and patent foramen ovale. *Curr Opin Cardiol*. 2008;23:537–44. <https://doi.org/10.1097/hco.0b013e32831311bd>.
49. Thomalla G, Cheng B, Ebinger M, et al. DWI-FLAIR mismatch for the identification of patients with acute ischaemic stroke within 4.5 h of symptom onset (PRE-FLAIR): a multicentre observational

- study. *Lancet Neurol.* 2011;10:978–86. [https://doi.org/10.1016/s1474-4422\(11\)70192-2](https://doi.org/10.1016/s1474-4422(11)70192-2).
50. Wardlaw JM, Murray V, Berge E, et al. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet.* 2012;379:2364–72. [https://doi.org/10.1016/s0140-6736\(12\)60738-7](https://doi.org/10.1016/s0140-6736(12)60738-7).
51. Wardlaw JM, Murray V, Berge E, et al. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2014. <https://doi.org/10.1002/14651858.cd000213.pub3>.
52. Wijidicks EFM, Sheth KN, Carter BS, et al. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014;45:1222–38. <https://doi.org/10.1161/01.str.0000441965.15164.d6>.